2. **(Reiterated)** A method for promoting survival of substantia nigra neuronal cells comprising contacting the cells with an effective amount of a lipophilic modified *hedgehog* polypeptide sufficient to promote the survival of substantia nigra neuronal cells.

3. **(Reiterated)** A method for promoting survival of dopaminergic cells comprising contacting the cells with an effective amount of a lipophilic modified *hedgehog* polypeptide sufficient to promote the survival of dopaminergic cells.

4. **(Reiterated)** A method for promoting survival of GABAergic cells comprising contacting the cells with an effective amount of a lipophilic modified *hedgehog* polypeptide sufficient to promote the survival of GABAergic cells.

11. **(Reiterated)** The method of any of claims 1-4, wherein the *hedgehog* polypeptide is modified with one or more fatty acid moieties.

REMARKS

Claims 1-21 constitute the pending claims in the present application. Applicants note that claims 5-10 and 12-21 have been withdrawn from consideration, and claims 1-4 and 11 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants apologize for the omission of matter from the response filed March 18, 2002. Specifically, claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beachy et al. and/or Ingham et al. in view of Muranishi et al. Applicants traverse this rejection.

MPEP 2141 outlines the criteria to be applied when assessing whether a claimed invention is unpatentable under 35 U.S.C. 103(a). "(A) the claimed invention must be considered as a whole; (B) the references must be considered as a whole and must suggest the

desirability and thus the obviousness of making the combination; (C) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) reasonable expectation of success is the standard with which obviousness is determined." Applicants contend that the cited combination of references fail to meet these criteria, and thus fail to render obvious the claimed invention.

The Office Action contends that since Beachy et al. and/or Ingham et al. teach that hedgehog polypeptides can promote neurogenesis, and Muranishi et al. teach the acylation of peptide hormones to improve their characteristics, one of skill in the art would have been motivated to combine the cited references to arrive at Applicants' invention. However, a closer analysis of Muranishi et al. demonstrates that one of skill in the art would not have had a reasonable expectation of success at arriving at Applicants' invention given the teachings of the cited references. Muranishi et al. teach the acylation of three peptide hormones: insulin, thyrotropin-releasing hormone (TRH), and tetragastrin (TG). The molecular weight of these peptide hormones is substantially less than that of the bioactive portion of a hedgehog protein. The molecular weights of the peptide hormones are: 362.4 for TRH, 596.7 for TG, and 5733.2 for insulin. Although the authors point out that they have chosen peptide hormones having a range of molecular weights, these molecular weights are still substantially smaller than that of a bioactive fragment of a hedgehog protein (approximately 19,000). Applicants point out that the molecular weight of a bioactive fragment of a hedgehog protein is greater than three times that of insulin, the largest peptide hormone tested by Muranishi et al.

The teachings of Muranishi et al. are directed to lipophilic modifications of small peptide hormones. The authors themselves point this fact out in describing their work. "The above studies using new analogues of three typical peptide hormones show that: (1) the peptide hormones, from tripeptide to polypeptides, with a molecular weight of 6000, can be derivatized to their lipophilic analogues by the chemical attachment of fatty acid moieties, and the resultant analogues maintain most of their original pharmacological activities." (page 187, column 1). Muranishi et al. neither teach nor suggest the lipophilic modification of polypeptides and proteins with molecular weights greater than 6000. Accordingly, given that Muranishi et al. fail to teach that larger proteins can be lipophilically modified to alter their characteristics, one of skill in the art would not have had a reasonable expectation of success in combining the cited

references to arrive at Applicants' invention. Absent Applicants' invention, one of skill in the art would not have predicted that large proteins, with a molecular weight greater than three times that of insulin, could be modified and used to promote survival or functional performance of neural tissue. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

David P. Halstead
Reg. No. 44,735

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Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050